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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

99870170.0

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Page 2 de l'attestation

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Demande n°
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Titre de l'invention
Interleukin-5 inhibiting 6-azauracil derivatives

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See for title page 1 of the description

NON-STEROIDAL IL-5 INHIBITORS, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

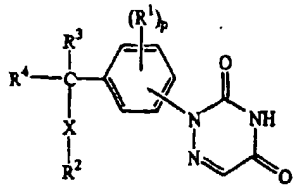
The present invention concerns IL-5 inhibiting 6-azauracil derivatives useful for treating eosinophil-dependent inflammatory diseases; to processes for their preparation and compositions comprising them. It further relates to their use as a medicine.

Eosinophil influx, leading to subsequent tissue damage, is an important pathogenic event in bronchial asthma and allergic diseases. The cytokine interleukin-5 (IL-5), produced mainly by T lymphocytes as a glycoprotein, induces the differentiation of eosinophils in bone marrow and, primes eosinophils for activation in peripheral blood and sustains their survival in tissues. As such, IL-5 plays a critical role in the process of eosinophilic inflammation. Hence, the possibility that inhibitors of IL-5 production would reduce the production, activation and/or survival of eosinophils provides a therapeutic approach to the treatment of bronchial asthma and allergic diseases such as, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and also other eosinophil-dependent inflammatory diseases.

Steroids, which strongly inhibit IL-5 production *in vitro*, have long been used as the only drugs with remarkable efficacy for bronchial asthma and atopic dermatitis, but they cause various serious adverse reactions such as diabetes, hypertension and cataracts. Therefore, it would be desirable to find non-steroidal compounds having the ability to inhibit IL-5 production in human T-cells and which have little or no adverse reactions.

US 4,631,278 discloses α-aryl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-benzeneacetonitriles and US 4,767,760 discloses 2-(substituted phenyl)-1,2,4-triazine-3,5(2*H*,4*H*)-diones, all having anti-protozoal activity, in particular, anti-coccidial activity. EP 831,088 discloses 1,2,4-triazine-3,5-diones as anticoccidial agents. WO99/02505 discloses 6-azauracil derivatives which prove to be potent inhibitors of the production of IL-5.

The present invention is concerned with the compounds of formula



(I)

the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein :

p represents an integer being 0, 1, 2, 3 or 4;

X represents O, S, NR^5 or a direct bond or-X-R^2 taken together may represent cyano;

Y represents O, S, NR^5, or $S(O)_2$;

each R^1 independently represents C(=0)-Z-R^{14}, C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or C_{1-4}alkyl substituted with C(=0)-Z-R^{14}, Het^3, R^6 or NR^7R^8;

R^2 represents Het^1, C_{3-7}cycloalkyl optionally substituted with C(=0)-Z-R^{14}, C_{1-6}alkyl or C_{1-6}alkyl substituted with one or two substituents selected from C(=0)-Z-R^{14}, hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxy optionally substituted with C(=0)-Z-R^{14}, C_{1-6}alkylsulfonyloxy, C_{3-7}cycloalkyl optionally substituted with C(=0)-Z-R^{14}, aryl, aryloxy, arylthio, Het^1, Het^1oxy and Het^1thio; and if X is O, S or NR^5, then R^2 may also represent aminothiocarbonyl, C_{1-4}alkylcarbonyl optionally substituted with C(=0)-Z-R^{14}, C_{1-4}alkylthiocarbonyl optionally substituted with C(=0)-Z-R^{14} , arylcarbonyl, arylthiocarbonyl, Het^1carbonyl or Het^1thiocarbonyl;

R^3 represents hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl;

R^4 represents hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl; or

R^3 and R^4 taken together form a C_{2-6}alkanediyl;

R^5 represents hydrogen or C_{1-4}alkyl;

each R^6 independently represents C_{1-6}alkylsulfonyl, aminosulfonyl, mono- or di-(C_{1-4}alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC_{1-6}alkylsulfonyl, C_{1-6}alkylsulfinyl, phenylC_{1-4}alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, *N*-C_{1-4}alkyl-*N*-piperidinylaminosulfonyl or mono-or di(C_{1-4}alkyl)aminoC_{1-4}alkylsulfonyl;

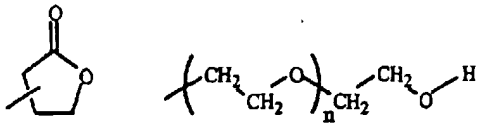
each R^7 and each R^8 are independently selected from hydrogen, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyl-carbonyl, arylcarbonyl, Het^3carbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-Z-R^{14}, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, Het^3 and R^6;

R^9 and R^{10} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, Het^3carbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-Z-R^{14}, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, Het^3 and R^6;

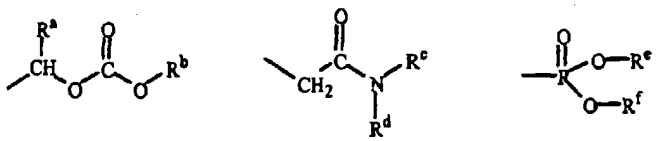
each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4}alkyloxy optionally substituted with C(=O)-Z-R^{14}, formyl, trihaloC_{1-4}alkylsulfonyloxy, R^6, NR^7R^8, C(=O)$NR^{15}R^{16}$, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, aryl, aryloxy, arylcarbonyl, C_{3-7}cycloalkyl optionally substituted with C(=O)-Z-R^{14}, C_{3-7}cycloalkyloxy optionally substituted with C(=O)-Z-R^{14}, phthalimide-2-yl, Het^3, Het^4 and C(=O)Het^3;

R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-Z-R^{14}, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14} and R^6;

each R^{14} independently represents C_{1-4} alkyl substituted with one or more substituents selected from phenyl, di-C_{1-4}alkylamino, cyano, Het^1 and C_{3-7} cycloalkyl, hydrogen, C_{1-20}acyl (having a straight or branched, saturated or unsaturated hydrocarbon chain having 1 to 20 carbon atoms), C_{1-20}alkyl, C_{3-7}cycloalkyl, polyhaloC_{1-20}alkyl or a radical of formula



(a) (b)

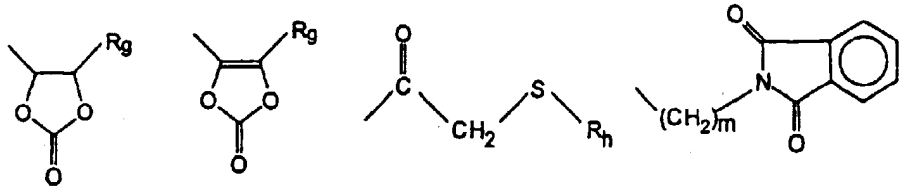


(c) (d) (e)

wherein n is 0 to 5;

R^a, R^b, R^c, R^d, R^e and R^f are each independently hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl; or

R^e and R^f taken together may form $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-CH_2-$; or a radical of formula



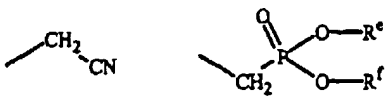
(h) (i) (j) (k)

wherein m is 1 to 4

R_g and R_h are each independently C_{1-4} alkyl;

each Z independently represents O, S, NH, $-CH_2-O-$ or $-CH_2-S-$ whereby $-CH_2-$ is attached to the carbonyl group;

$-Z-R^{14}$ taken together form a radical of formula



(f) (g)

R^{15} and R^{16} are each independently selected from dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, $-C(=O)-Z-R^{14}$, arylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, pyridinylC_{1-4}alkyl, Het^3 or R^6;

aminocarbonylmethylene or mono-or di(C_{1-4}alkyl)aminocarbonylmethylene;

aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, cyano, halo, hydroxy, C_{1-4}alkyl, C_{3-7}cyclo-alkyl, C_{1-4}alkyloxy, formyl, polyhaloC_{1-4}alkyl, NR^9R^{10}, $C(=O)NR^9R^{10}$, $C(=O)$-Z-R^{14}, R^6, -O-R^6, phenyl, Het^3, $C(=O)Het^3$ and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C_{1-4}alkyloxy, $C(=O)$-Z-R^{14}, -Y-C_{1-4}alkanediyl-$C(=O)$-Z-R^{14}, Het^3 or NR^9R^{10};

Het^1 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from Het^2 and R^{11};

Het^2 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from R^{11};

Het^3 represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, piperidinyl, $NR^{12}R^{13}$, C(=O)-Z-R^{14}, R^6 and C_{1-4}alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4}alkyloxy, phenyl, C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, R^6 and $NR^{12}R^{13}$;

Het^4 represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl provided however that

- R^2 is other than C_{1-6} alkyloxycarbonylC_{1-6}alkyl, aminocarbonyl; and
- R^7, R^8, R^9 and R^{10} are other than aminocarbonyl, C_{1-4}alkylcarbonyloxy- C_{1-4}alkylcarbonyl, hydroxy C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl C(=O)-O-R^{14}, C_{1-4}alkanediylC(=O)-O-R^{14} and –Y-C_{1-4}alkanediylC(=O)-O-R^{14}; and
- R^{12} and R^{13} are other than C_{1-4}alkylcarbonyloxy-C_{1-4}alkylcarbonyl, hydroxy C_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonylcabonyl; and
- R^{11} is other than C(=O)-O-R^{14}, Y-C_{1-4}alkanediyl – C(=O)-OR^{14}, $C(=O)NH_2$, $C(=O)NHC_{1-4}$alkyl or $C(=O)NHC_{3-7}$cycloalkyl; and
- R^{14} is other than hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, aminocarbonylmethylene, mono- or di (C_{1-4}alkyl) aminocarbonylmethylene in the event Z is 0; and
- R^{15} and R^{16} are other than aminocarbonyl, C_{1-4}alkylcarbonyloxy-C_{1-4}alkylcarbonyl, hydroxy C_{1-4}alkylcarbonyl or C_{1-4}alkyloxycarbonylcarbonyl; and
- Aryl is other than phenyl substituted with C(=O)-O-R^{14} $C(=O)NH_2$, $C(=O)NHC_{1-4}$alkyl, $C(=O)NHC_{3-7}$cycloalkyl and/or with C_{1-4}alkyl substituted with C(=O)-O-R^{14} or Y-C_{1-4}alkanediyl – C(=O)-O-R^{14}; and
- Het^3 is other than a monocyclic heterocycle substituted with C(=O)·O-R^{14} and/or with C_{1-4}alkyl substituted with C(=O)-O-R^{14} and/or Y-C_{1-4}alkanediyl – (=O)-O-R^{14}; and
- The said compound of formula (I) contains at least one – C(=O)-Z-R^{14} moiety.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl,

cyclohexyl and cycloheptyl; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl, 2,2-dimethylethyl and the like; C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like C_{1-20}alkyl is meant to include C_{1-6}alkyl and the higher homologues thereof having 7 to 20 carbon atoms such as, for example, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl, nonadecyl, eicosyl and the like C_{5-20}alkyl is meant to include C_{1-20}alkyl except for C_{1-4}alkyl; polyhaloC_{1-4}alkyl is defined as polyhalosubstituted C_{1-4}alkyl, in particular C_{1-4}alkyl substituted with 1 to 6 halogen atoms, more in particular difluoro- or trifluoromethyl; polyhaloC_{1-6}alkyl is defined as polyhalosubstituted C_{1-6}alkyl; polyhaloC_{1-20}alkyl is defined as polyhalosubstituted C_{1-20}alkyl. The term C_{1-4}alkanediyl defines bivalent straight or branch chained alkanediyl radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; C_{2-6}alkanediyl defines bivalent straight or branch chained alkanediyl radicals having from 2 to 6 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the like.

Het^1, Het^2, Het^3 and Het^4 are meant to include all the possible isomeric forms of the heterocycles mentioned in the definition of Het^1, Het^2, Het^3 and Het^4, for instance, pyrrolyl also includes 2*H*-pyrrolyl; triazolyl includes 1,2,4-triazolyl and 1,3,4-triazolyl; oxadiazolyl includes 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl and 1,3,4-oxadiazolyl; thiadiazolyl includes 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl and 1,3,4-thiadiazolyl; pyranyl includes 2*H*-pyranyl and 4*H*-pyranyl.

The heterocycles represented by Het^1, Het^2, Het^3 and Het^4 may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heterocycle is imidazolyl, it may be a 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and 5-imidazolyl; when it is thiazolyl, it may be 2-thiazolyl, 4-thiazolyl and 5-thiazolyl; when it is triazolyl, it may be 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,3,4-triazol-1-yl and 1,3,4-triazol-2-yl; when it

is benzthiazolyl, it may be 2-benzthiazolyl, 4-benzthiazolyl, 5-benzthiazolyl, 6-benzthiazolyl and 7-benzthiazolyl.

The C_{1-20}acyl is derived from

acetic acid	CH_3COOH		tridecanoic acid	$C_{12}H_{25}COOH$
propionic acid	C_2H_5COOH		myristic acid	$C_{13}H_{27}COOH$
butyric acid	C_3H_7COOH		pentadecanoic acid	$C_{14}H_{29}COOH$
valeric acid	C_4H_9COOH		palmitic acid	$C_{15}H_{31}COOH$
hexanoic acid	$C_5H_{11}COOH$		heptadecanoic acid	$C_{16}H_{33}COOH$
heptanoic acid	$C_6H_{13}COOH$		stearic acid	$C_{17}H_{35}COOH$
octanoic acid	$C_7H_{15}COOH$		oleic acid	$C_{17}H_{33}COOH$
nonanoic acid	$C_8H_{17}COOH$		linolic acid	$C_{17}H_{31}COOH$
decanoic acid	$C_9H_{19}COOH$		linolenic acid	$C_{17}H_{29}COOH$
undecanoic acid	$C_{10}H_{21}COOH$		nonadecanoic acid	$C_{18}H_{37}COOH$
lauric acid	$C_{11}H_{23}COOH$		icosanoic acid	$C_{19}H_{39}COOH$

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxy-acetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzene-sulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium,

sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide. For example, one or more nitrogen atoms of any of the heterocycles in the definition of Het^1, Het^2 and Het^3 may be *N*-oxidized.

Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For example, a hydroxy substituted triazine moiety may also exist as the corresponding triazinone moiety; a hydroxy substituted pyrimidine moiety may also exist as the corresponding pyrimidinone moiety.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms in which the compounds of formula (I) can exist. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration, used herein in accordance with Chemical Abstracts nomenclature. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

The compounds of formula (I) and some of the intermediates in the present invention contain one or more asymmetric carbon atoms. The pure and mixed stereochemically isomeric forms of the compounds of formula (I) are intended to be embraced within the scope of the present invention.

Whenever used hereinafter, the term "compounds of formula (I)" is meant to also include their *N*-oxide forms, their pharmaceutically acceptable addition salts, and their stereochemically isomeric forms.

An interesting group of compounds are those compounds of formula (I) wherein the 6-azauracil moiety is connected to the phenyl ring in the para or meta position relative to the carbon atom bearing the -X-R^2, R^3 and R^4 substituents; preferably in the para position.

Another interesting group contains those compounds of formula (I) wherein one or more of the following restrictions apply :

- p is 0, 1 or 2;
- X is S, NR^5, or a direct bond; more in particular NH or a direct bond;
- each R^1 independently is halo, polyhaloC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkyloxy or aryl, preferably, chloro or trifluoromethyl, more preferably chloro;
- R^2 is Het^1 or C_{1-6}alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino, C(=0)-Z-R^{14} C_{1-6}alkyloxy optionally substituted with C(=0)-Z-R^{14}, C_{1-6}alkylsulfonyloxy, C_{3-7}cycloalkyl optionally substituted with C(=0)-Z-R^{14}, aryl, aryloxy, arylthio, Het^1, Het^1oxy and Het^1thio; and if X is O, S or NR^5, then R^2 may also represent aminothiocarbonyl, C_{1-4}alkylcarbonyl optionally substituted with C(=0)-Z-R^{14}, C_{1-4}alkylthiocarbonyl optionally substituted with C(=0)-Z-R^{14}, arylcarbonyl, arylthiocarbonyl, Het^1carbonyl or Het^1thiocarbonyl; particularly R^2 is Het^1 or in the event X is NH, R^2 may also be aminothiocarbonyl or Het^1carbonyl;
- R^3 is hydrogen, methyl, ethyl, propyl or cyclohexyl; preferably, methyl;
- R^4 is hydrogen or methyl; preferably, methyl;
- R^3 and R^4 are taken together to form a 1,4-butanediyl;
- R^6 is C_{1-6}alkylsulfonyl or aminosulfonyl;
- R^7 and R^8 are each independently hydrogen, C_{1-4}alkyl, Het^3 or R^6;
- R^9 and R^{10} are each independently hydrogen, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, aminocarbonyl, Het^3carbonyl, Het^3 or R^6;

- R^{11} is cyano, nitro halo, C_{1-4}alkyloxy, formyl, NR^7R^8, $C(=O)NR^{15}R^{16}$, $-C(=O)-Z-R^{14}$, aryl, arylcarbonyl, Het^3, Het^4 and $C(=O)Het^3$;
- R^{14} isdihydrofuranyl, C_{5-20}alkyl, C_{1-4}alkyl substituted with one or more substituents selected from phenyl, C_{1-4}alkylamino, cyano, Het^1 and C_{3-7}cycloalkyl;
- aryl is phenyl optionally substituted with one, two or three substituents each independently selected from nitro, cyano, halo, hydroxy, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}alkyloxy, formyl, polyhaloC_{1-4}alkyl, NR^9R^{10}, $C(=O)NR^9R^{10}$, $C(=O)-O-R^{14}$, $-O-R^6$, phenyl, $C(=O)Het^3$ and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C_{1-4}alkyloxy, $C(=O)-Z-R^{14}$, Het^3 or NR^9R^{10};
- Het^1 is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with Het^2 or R^{11}; preferably Het^1 is imidazolyl, oxadiazolyl, thiazolyl or pyridinyl each independently and optionally substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with Het^2 or R^{11};
- Het^2 is an aromatic heterocycle; more in particular furanyl, thienyl, pyridinyl or benzothienyl, wherein said aromatic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R^{11} and C_{1-4}alkyl;
- Het^3 is piperidinyl, piperazinyl, morpholinyl and tetrahydropyranyl each independently and optionally substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4}alkyl, C_{1-4}alkylcarbonyl, piperidinyl and C_{1-4}alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4}alkyloxy and phenyl;
- Het^4 is thienyl.

Special compounds are those compounds of formula (I) wherein p is 2 and both R^1 substituents are chloro; more preferably the two chloro substituents are in the ortho positions relative to the carbon atom bearing the -X-R^2, R^3 and R^4 substituents.

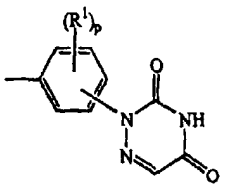
Particular compounds are those compounds of formula (I) wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R^2, R^3 and R^4 substituents, and p is 2 whereby both R^1 substituents are chloro positioned ortho relative to the carbon atom bearing the -X-R^2, R^3 and R^4 substituents.

Other particular compounds are those compounds of formula (I) wherein X is a direct bond and R^2 is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with Het^2 or R^{11}; more in particular R^2 is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.

Preferred compounds are those compounds of formula (I) wherein R^3 and R^4 are both methyl and -X-R^2 is Het^1 wherein Het^1 suitably is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.

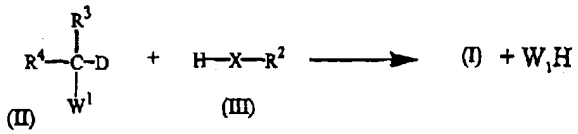
More preferred compounds are those compounds of formula (I) wherein R^3 and R^4 are both methyl, -X-R^2 is optionally substituted 2-thiazolyl or 3-oxadiazolyl, the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R^2, R^3 and R^4 substituents, and p is 2 whereby both R^1 substituents are chloro positioned ortho relative to the carbon atom bearing the -X-R^2, R^3 and R^4 substituents.

In order to simplify the structural representation of the compounds of formula (I), the group



will hereinafter be represented by the symbol D.

Compounds of formula (I) can generally be prepared by reacting an intermediate of formula (II) wherein W^1 is a suitable leaving group such as, for example, a halogen atom, with an appropriate reagent of formula (III).



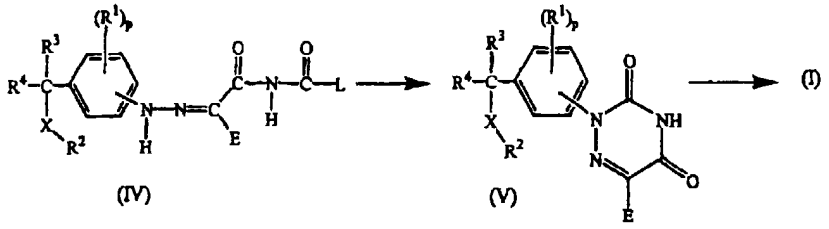
Said reaction may be performed in a reaction-inert solvent such as, for example, acetonitrile, *N,N*-dimethylformamide, acetic acid, tetrahydrofuran, ethanol or a mixture thereof. Alternatively, in case the reagent of formula (III) acts as a solvent, no additional reaction-inert solvent is required. The reaction is optionally carried out in the presence of a base such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium bicarbonate, sodiumethanolate and the like. Convenient reaction temperatures range between -70°C and reflux temperature.

In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

Some of the compounds and intermediates of the present invention can be prepared according to or analogous to the procedures described in EP-A-0,170,316, EP-A-0,232,932 and WO99/02505.

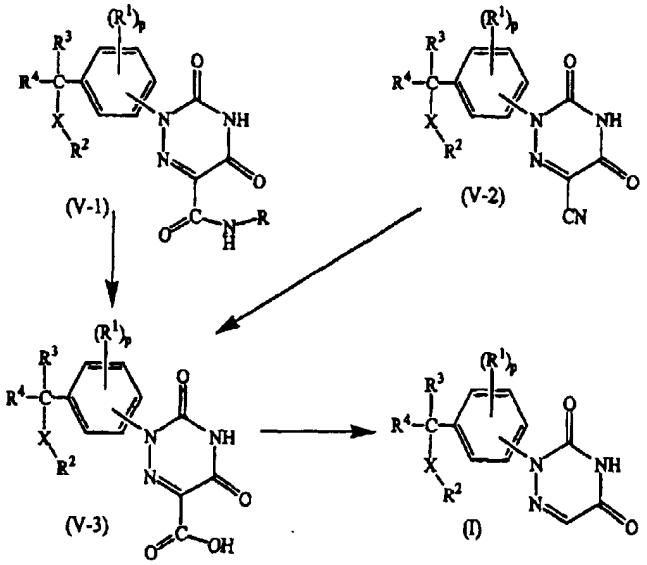
Alternatively, for instance, compounds of formula (I) may generally be prepared by cyclizing an

intermediate of formula (IV) wherein L is a suitable leaving group such as, for example, C_{1-6}alkyloxy or halo, and E represents an appropriate electron attracting group such as, for example, an ester, an amide, a cyanide, C_{1-6}alkylsulfonyloxy and the like groups; and eliminating the group E of the thus obtained triazinedione of formula (V). The cyclization can suitably be carried out by refluxing the intermediate (IV) in acidic medium such as acetic acid and in the presence of a base such as, for example, potassium acetate.



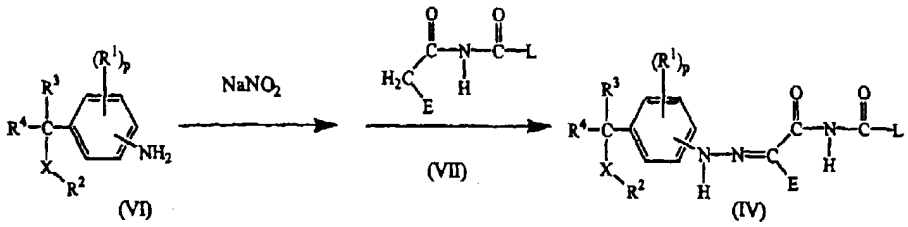
(IV) (V) (I)

Depending on its nature, E can be eliminated using various art-known elimination procedures. For example when E is an amide or a cyano moiety, it can be hydrolized to a carboxylic moiety by for instance refluxing the intermediate bearing the E group in hydrochloric acid and acetic acid. The thus obtained intermediate can then be further reacted with mercaptoacetic acid or a functional derivative thereof to obtain a compound of formula (I). Said reaction is conveniently carried out at elevated temperatures ranging up to reflux temperature.



(V-1) (V-2) (V-3) (I)

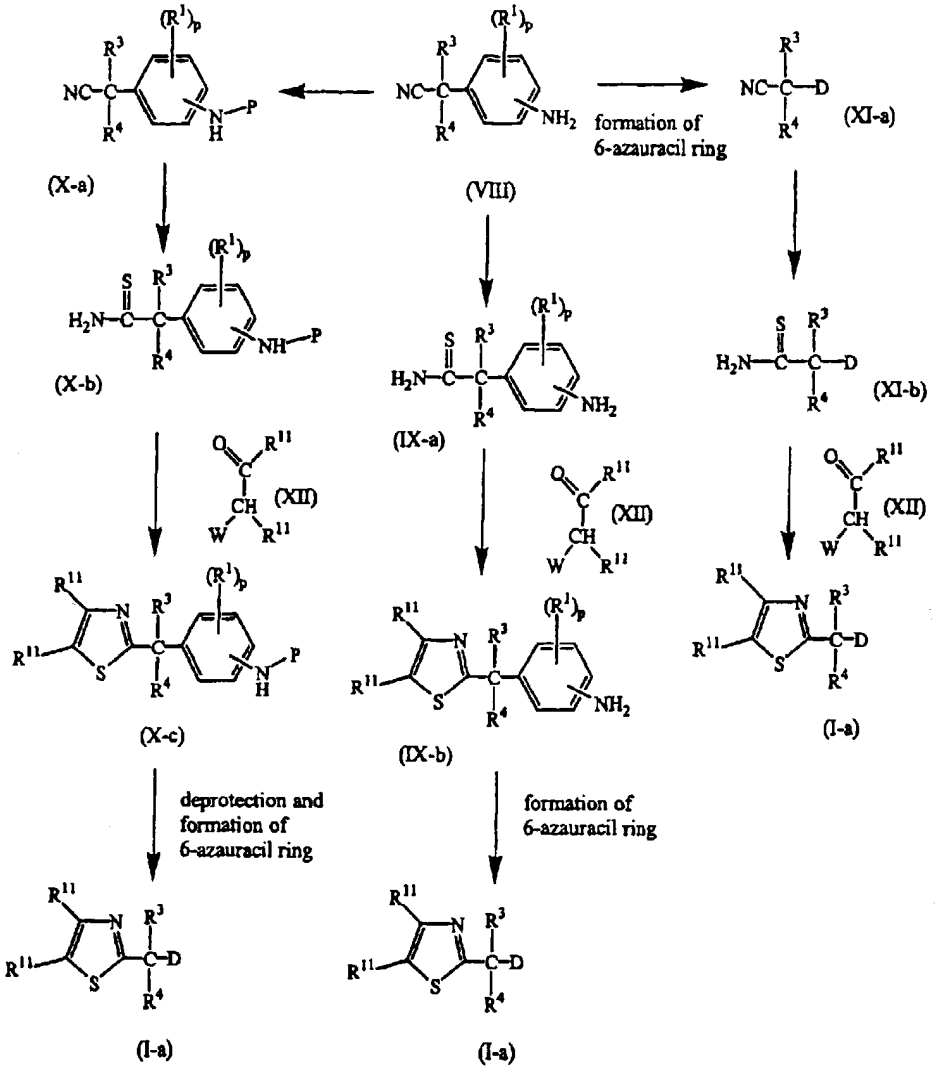
A suitable way to prepare intermediates of formula (IV) involves the reaction of an intermediate of formula (VI) with sodium nitrate or a functional derivative thereof in an acidic medium such as for example hydrochloric acid in acetic acid, and preferably in the same reaction mixture, further reacting the thus obtained intermediate with a reagent of formula (VII) wherein L and E are as defined above, in the presence of a base such as, for example, sodium acetate.



An interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R^2 is an optionally substituted 2-thiazolyl moiety, said compounds being represented by formula (I-a). The optionally substituted 2-thiazolyl moiety can be incorporated in the compounds of formula (I-a) at different stages of the preparation process.

For instance, scheme 1 depicts three possible ways to prepare compounds of formula (I-a).

Scheme 1



A first pathway involves the reaction of the cyano moiety in an intermediate of formula (VIII) to the corresponding thioamide using H_2S gas in a suitable solvent such as, for example, pyridine and in the presence of a base such as, for example, triethylamine, thus obtaining an intermediate of formula (IX-a). This thioamide can then be cyclized with an intermediate of formula (XII) wherein W is a suitable leaving group such as, for example, a halogen, e.g. bromo, in a suitable solvent such as, for example, ethanol. The amino moiety in the resulting 2-thiazolyl derivative of formula (IX-b) can then be further reacted as described hereinabove to form a 6-azauracil ring, thus obtaining a compound of formula (I-a).

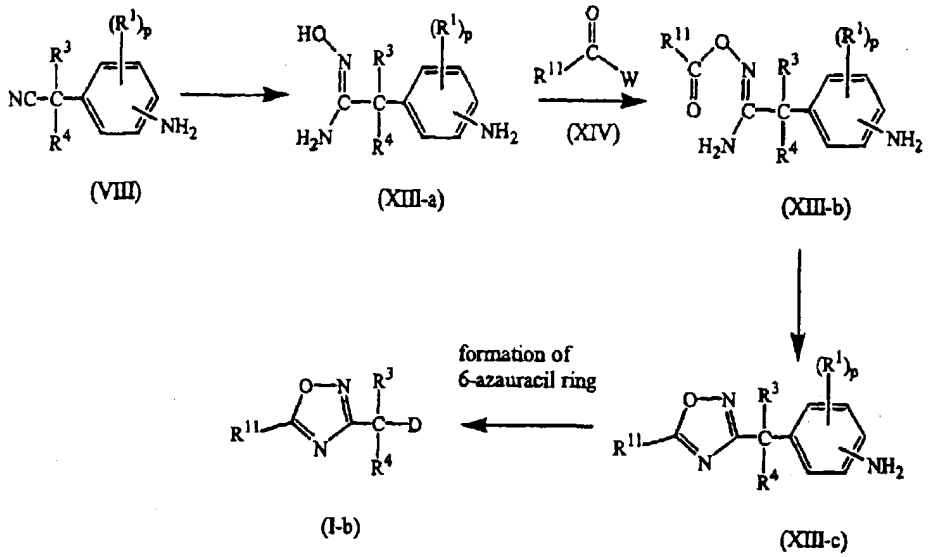
A second pathway to form compounds of formula (I-a) involves first the protecting of the amino moiety in an intermediate of formula (VIII) by introducing a suitable protective group P such as, for example, an alkylcarbonyl group, using art-known protection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (VII) can be reacted with the corresponding anhydride of formula alkyl-C(=O)-O-C(=O)-alkyl in an appropriate solvent such as, for example, toluene. The thus obtained intermediate of formula (X-a) can then be further reacted according to the first pathway described hereinabove. The final step, before formation of the 6-azauracil ring can be initiated after having deprotected the amino moiety using art-known deprotection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (X-c) may be deprotected by reacting them in a suitable solvent such as, for example, ethanol, in the presence of an acid such as, for example, hydrochloric acid.

A third pathway involves first the formation of the 6-azauracil ring as described hereinabove but starting from an intermediate of formula (VIII), and subsequently reacting the thus formed intermediate of formula (XI-a) with H_2S and further reacting the thioamide of formula (XI-b) with an intermediate of formula (XII) as described in the first pathway, to finally form a compound of formula (I-a).

Another interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R^2 is an optionally substituted 1,2,4-oxadiazol-3-yl moiety, said compounds being represented by formula (I-b-1). The optionally substituted 1,2,4-oxadiazol-3-yl moiety can be incorporated at the same stages of the reaction procedure as depicted for the 2-thiazolyl derivatives in scheme 1.

For instance, analogous to one of the three pathways shown in scheme 1, compounds of formula (I-b) can be performed by reacting an intermediate of formula (VIII) as depicted in scheme 2.

Scheme 2

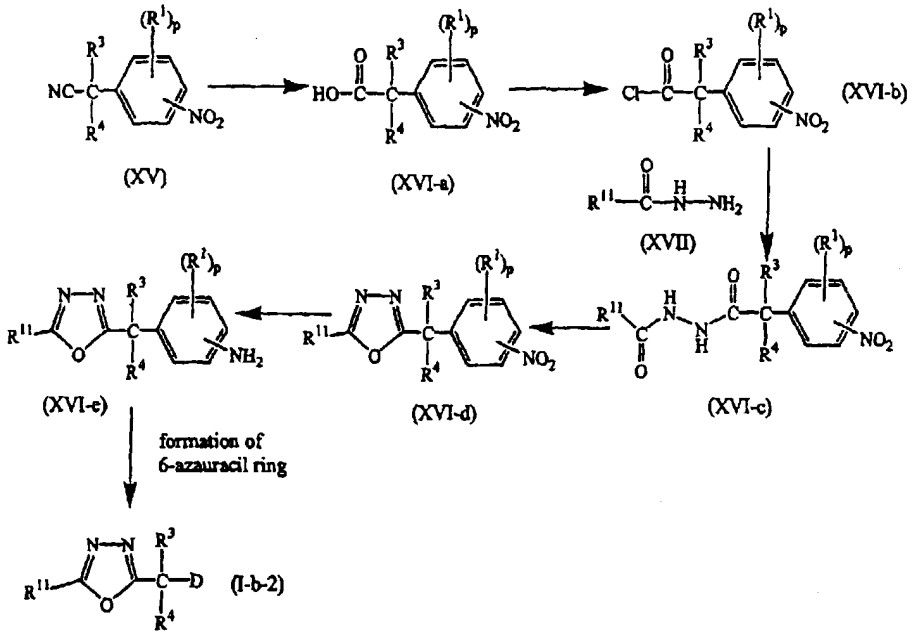


In said scheme 2, the cyano group of an intermediate of formula (VIII) is reacted with hydroxylamine or a functional derivative thereof in a suitable solvent such as, for example, methanol, and in the presence of a base such as, for example sodium methanolate. The thus formed intermediate of formula (XIII-a) is then reacted with an intermediate of formula (XIV) wherein W is a suitable leaving group such as, for example, a halogen, e.g. chloro, in an appropriate solvent such as, for example, dichloromethane, and in the presence of a base, such as, for example, *N,N*-(1-methyl-ethyl)ethaneamine. The resulting intermediate of formula (XIII-b) is then cyclized to a 3-oxadiazolyl derivative of formula (XIII-c). The amino moiety in the intermediates of formula (XIII-c) can then be transformed to the 6-azauracil ring as described above.

Still another interestng subgroup within the present invention are those compounds of formula (I) wherein -X-R^2 is an optionally substituted 1,3,4-oxadiazol-2-yl moiety, said compounds being represented by formula (I-b-2).

For instance, compounds of formula (I-b-2) can be prepared as depicted in scheme 3.

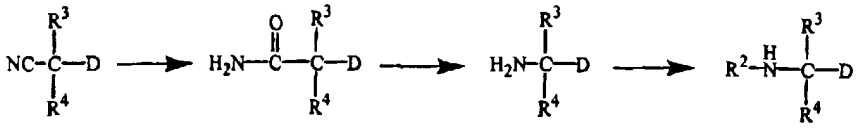
Scheme 3



The nitrile moiety in an intermediate of formula (XV) is transformed into a carboxylic acid moiety using art-known techniques. For instance, the nitrile derivative may be refluxed in a mixture of sulfuric acid and acetic acid in water. The carboxylic acid derivative of formula (XVI-a) may the further be reacted with a chlorinating agent such as, for example, thionyl chloride, to form an acylchloride derivative of formula (XVI-b). Subsequently, The acyl chloride may be reacted with a hydrazine derivative of formula (XVII) in a suitable solvent such as, for example, dichloromethane, and in the presence of a base such as, for example *N,N*-(1-methylethyl)ethaneamine. The thus formed intermediate of formula (XVI-c) may be cyclized to a 1,2,4-oxadiazol-2-yl derivative of formula (XVI-d) in the presence of phophoryl chloride.As a final step before the formation of the 6-azauracil ring as described above, the nitro group in the intermediates of formula (XVI-e) is reduced to an amino group using art-known reduction techniques such as, for instance, reducing the nitro group with hydrogen in methanol and in the presnece of a catalyst such as Raney Nickel.

Yet another interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R^2 is -NH-R^2, said compounds being represented by formula (I-c-1). Scheme 4 depicts a suitable pathway to obtain compounds of formula (I-c-1).

Scheme 4

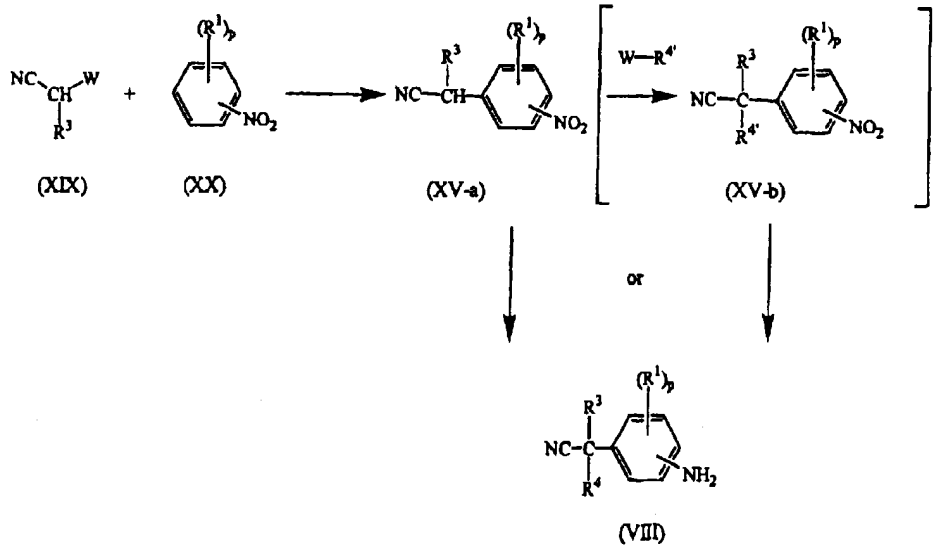


(XI-a) (XVIII-a) (XVIII-b) (I-c-1)

In said scheme 4, the cyano moiety of an intermediate of formula (XI-a) is hydrolized to the corresponding amide using art-known techniques such as, for instance, hydrolysis in the presence of acetic acid and sulfuric acid. The thus formed amide in the intermediates of formula (XVIII-a) can be transformed in an amine using (diacetoxyiodo)benzene or a functional derivative thereof in a suitable solvent such as, for example a mixture of water and acetonitrile. The amine derivative of formula (XVIII-b) can then be reacted with benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate as described in Tetrahedron Letters No.14 (1975) 1219-1222 to obtain a compound, or with a functional derivative thereof such as, for instance, an isothiocyanate, in an appropriate solvent such as, for example, tetrahydrofuran.

Intermediates of formula (VIII) can be prepared as depicted in scheme 5.

Scheme 5



(XIX) (XX) (XV-a) (XV-b) (VIII)

An intermediate of formula (XIX) and an intermediate of formula (XX) may be reacted in a suitable solvent such as, for example, dimethylsulfoxide, in the presence of a base

such as, for example sodium hydroxide, to form an intermediate of formula (XV-a). The nitro moiety in the intermediates of formula (XV-a) may either be immediately reduced to an amino group using art-known reduction techniques such as, for example, reducing the nitro group with hydrogen in methanol and in the presnece of a catalyst such as Raney Nickel, or may first be reacted with an intermediate of formula $R^{4'}$-W wherein $R^{4'}$ is the same as R^4 but other than hydrogen and W is a suitable leaving group such as, for example, a halogen, e.g. iodo, in a suitable solvent such as, for example, *N*,*N*-dimethylformamide, and in the presence of a suitable base such as, for example, sodium hydride, before reducing the nitro moiety.

The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation such as, for example, those mentioned in WO99/02505 and the ones exemplified in the experimental part hereinafter.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

Some of the intermediates and starting materials as used in the reaction procedures mentioned hereinabove are known compounds and may be commercially available or may be prepared according to art-known procedures.

IL-5, also known as eosinophil differentiating factor (EDF) or eosinophil colony stimulating factor (Eo-CSF), is a major survival and differentiation factor for eosinophils and therefore thought to be a key player in eosinophil infiltration into tissues. There is ample evidence that eosinophil influx is an important pathogenic event in bronchial asthma and allergic diseases such as, cheilitis, irritable bowel disease, eczema, urticaria, vasculitis, vulvitis, winterfeet, atopic dermatitis, pollinosis, allergic rhinitis and allergic conjunctivitis; and other inflammatory diseases, such as eosinophilic syndrome, allergic angiitis, eosinophilic fasciitis, eosinophilic pneumonia,

PIE syndrome, idiopathic eosinophilia, eosinophilic myalgia, Crohn's disease, ulcerative colitis and the like diseases.

The present compounds also inhibit the production of other chemokines such as monocyte chemotactic protein-1 and -3 (MCP-1 and MCP-3). MCP-1 is known to attract both T-cells, in which IL-5 production mainly occurs, and monocytes, which are known to act synergetically with eosinophils (Carr et al., 1994, Immunology, *91*, 3652-3656). MCP-3 also plays a primary role in allergic inflammation as it is known to mobilize and activate basophil and eosinophil leukocytes (Baggiolini et al., 1994, Immunology Today, 15(3), 127-133).

The present compounds have no or little effect on the production of other chemokines such as IL-1, IL-2, Il-3, IL-4, IL-6, IL-10, γ-interferon (IFN-γ) and granulocyte-macrophage colony stimulating factor (GM-CSF) indicating that the present IL-5 inhibitors do not act as broad-spectrum immunosuppressives.

The selective chemokine inhibitory effect of the present compounds can be demonstrated by *in vitro* chemokine measurements in human blood. *In vivo* observations such as the inhibition of eosinophilia in mouse ear, the inhibition of blood eosinophilia in the *Ascaris* mouse model; the reduction of serum IL-5 protein production and splenic IL-5 mRNA expression induced by anti-CD3 antibody in mice and the inhibition of allergen- or Sephadex-induced pulmonary influx of eosinophils in guinea-pig are indicative for the usefulness of the present compounds in the treatment of eosinophil-dependent inflammatory diseases.

The present inhibitors of IL-5 production are particularly useful for administration via inhalation.

The intermediates of formula (XI-a) are interesting intermediates. Not only have they a particular usefulness as intermediates in the preparation of the compounds of formula (I), they also have valuable pharmacological activity.

In view of the above pharmacological properties, the compounds of formula (I) can be used as a medicine. In particular, the present compounds can be used in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases as mentioned hereinabove, more in particular bronchial asthma, atopic dertmatitis, allergic rhinitis and allergic conjunctivitis.

In view of the utility of the compounds of formula (I), there is provided a method of treating warm-blooded animals, including humans, suffering from eosinophil-dependent inflammatory diseases, in particular bronchial asthma, atopic dertmatitis, allergic rhinitis and allergic conjunctivitis. Said method comprises the systemic or topical administration of an effective amount of a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable addition salt or a possible stereoisomeric form thereof, to warm-blooded animals, including humans.

The present invention also provides compositions for treating eosinophil-dependent inflammatory diseases comprising a therapeutically effective amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for systemic administration such as parenteral administration; or topical administration such as via inhalation, a nose spray or the like. Application of said compositions may be by aerosol, e.g. with a propellent such as nitrogen, carbon dioxide, a freon, or without a propellent such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab. In particular, semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage.

Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In order to enhance the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions. In the preparation of aqueous compositions, addition salts of the subject compounds are obviously more suitable due to their increased water solubility.

Appropriate cyclodextrins are α-, β-, γ-cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6}alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-CD; hydroxyC_{1-6}alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxyC_{1-6}alkyl, particularly carboxymethyl or carboxyethyl; C_{1-6}alkylcarbonyl, particularly acetyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl or carboxy-C_{1-6}alkyloxyC_{1-6}alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β-CD, randomly methylated β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD (2-HP-β-CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The M.S.value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the M.S. ranges from 0.125 to 10.

The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The D.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the D.S. ranges from 0.125 to 3.

Due to their high degree of selectivity as IL-5 inhibitors, the compounds of formula (I) as defined above, are also useful to mark or identify receptors. To this purpose, the compounds of the present invention need to be labelled, in particular by replacing, partially or completely, one or more atoms in the molecule by their radioactive isotopes. Examples of interesting labelled compounds are those compounds having at least one halo which is a radioactive isotope of iodine, bromine or fluorine; or those compounds having at least one ^{11}C-atom or tritium atom.

One particular group consists of those compounds of formula (I) wherein R^3 and/or R^4 are a radioactive halogen atom. In principle, any compound of formula (I) containing a halogen atom is prone for radiolabelling by replacing the halogen atom by a suitable isotope. Suitable halogen radioisotopes to this purpose are radioactive iodides, e.g. ^{122}I, ^{123}I, ^{125}I, ^{131}I; radioactive bromides, e.g. ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br, and radioactive fluorides, e.g. ^{18}F. The introduction of a radioactive halogen atom can be performed by a suitable exchange reaction or by using any one of the procedures as described hereinabove to prepare halogen derivatives of formula (I).

Another interesting form of radiolabelling is by substituting a carbon atom by a ^{11}C-atom or the substitution of a hydrogen atom by a tritium atom.

Hence, said radiolabelled compounds of formula (I) can be used in a process of specifically marking receptor sites in biological material. Said process comprises the

steps of (a) radiolabelling a compound of formula (I), (b) administering this radiolabelled compound to biological material and subsequently (c) detecting the emissions from the radiolabelled compound. The term biological material is meant to comprise every kind of material which has a biological origin. More in particular this term refers to tissue samples, plasma or body fluids but also to animals, specially warm-blooded animals, or parts of animals such as organs.

The radiolabelled compounds of formula (I) are also useful as agents for screening whether a test compound has the ability to occupy or bind to a particular receptor site. The degree to which a test compound will displace a compound of formula (I) from such a particular receptor site will show the test compound ability as either an agonist, an antagonist or a mixed agonist/antagonist of said receptor.

When used in *in vivo* assays, the radiolabelled compounds are administered in an appropriate composition to an animal and the location of said radiolabelled compounds is detected using imaging techniques, such as, for instance, Single Photon Emission Computerized Tomography (SPECT) or Positron Emission Tomography (PET) and the like. In this manner the distribution of the particular receptor sites throughout the body can be detected and organs containing said receptor sites can be visualized by the imaging techniques mentioned hereinabove. This process of imaging an organ by administering a radiolabelled compound of formula (I) and detecting the emissions from the radioactive compound also constitutes a part of the present invention.

In general, it is contemplated that a therapeutically effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, in particular from 0.05 mg/kg to 10 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between two or four intakes per day.

Experimental part

In the examples hereinafter, "DMSO" stands for dimethylsulfoxide, "RT" stands for room temperature, "DMF" stand for *N,N*-dimethylformamide, "EtOAc" stands for ethylacetate, "DIPE" stands for diisopropylether and "THF" stands for tetrahydrofuran.

A. Preparation of the intermediate compounds

Example A1

a) A mixture of 2-chloropropionenitrile (0.2 mol) and 1,3-dichloro-5-nitrobenzene (0.2 mol) in DMSO (50ml) was added dropwise at RT to a solution of NaOH (1 mol) in DMSO (150ml) while the temperature was kept below 30°C. The mixture was stirred at RT for 1 hour, then poured out on ice and acidified with HCl. The precipitate was filtered off, washed with H_2O and taken up in CH_2Cl_2. The organic solution was washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/cyclohexane 70/30). The pure fractions were collected and the solvent was evaporated, yielding 19.5 g (40%) of (±)-2,6-dichloro-α-methyl-4-nitrobenzeneacetonitrile (interm. 1).

b) NaH 80% (0.0918 mol) was added portionwise at 0°C under N_2 flow to a solution of intermediate (1) (0.0612 mol) in DMF (100ml). The mixture was stirred at 0°C under N_2 flow for 1 hour. CH_3I (0.0918 mol) was added dropwise at 0°C. The mixture was stirred at 50°C for 12 hours, then poured out on ice and extracted with EtOAc. The organic layer was separated, washed with H_2O, dried, filtered and the solvent was evaporated, yielding 17.1g of 2,6-dichloro-α,α-dimethyl-4-nitrobenzeneacetonitrile (interm. 2).

c) A mixture of intermediate (2) (0.066 mol) in CH_3OH (200ml) was hydrogenated at RT under a 3 bar pressure for 1 hour with Raney Nickel (15g) as a catalyst. After uptake of H_2, the catalyst was filtered through celite, washed with CH_3OH and the filtrate was evaporated, yielding 17.1g of 4-amino-2,6-dichloro-α,α-dimethylbenzene-acetonitrile (interm. 3).

Example A2

a) A solution of $NaNO_2$ (0.36 mol) in H_2O (50 ml) was added to a solution of intermediate (3) (0.34 mol) in acetic acid (700 ml) and HCl (102 ml), stirred at 10°C. The reaction mixture was stirred for 80 minutes at 10°C. A powdered mixture of sodium acetate (1.02 mol) and diethyl(1,3-dioxo-1,3-propanediyl)biscarbamate (0.374 mol) was added and the reaction mixture was stirred for 40 minutes. The reaction mixture was poured out onto crushed ice. The precipitate was filtered off, washed with water, taken up into CH_2Cl_2, and the layers were separated. The organic layer was dried, filtered and the solvent evaporated, yielding 138.5 g (84%) of diethyl *N,N'*-

[2-[[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]hydrazono]-1,3-dioxo-1,3-propanediyl]dicarbamate (interm. 4).

b) A solution of intermediate (4) (0.28 mol) and potassium acetate (0.28 mol) in acetic acid (1000 ml) was stirred and refluxed for 3 hours. The reaction mixture containing ethyl [[2-[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-6-yl]carbonyl]carbamate (interm. 5) was used as such in the next step.

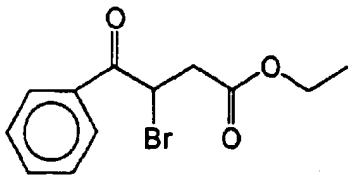
c) Intermediate (5) (crude reaction mixture) was treated with HCl 36% (0.84 mol). The reaction mixture was stirred and refluxed for 4 hours, then stirred at RT over the weekend. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated, yielding 111.6 g of 2-[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 6).

d) A suspension of intermediate (6) (0.28 mol) in mercaptoacetic acid (250.0 ml) was stirred for 4 hours at 100 °C, then allowed to cool to RT and stirred overnight. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated. Toluene was added and azeotroped on the rotary evaporator. The residue was purified by short column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed with DIPE, then dried, yielding 36.8 g (41%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α,α-dimethylbenzeneacetonitrile. The filtrate was stirred in DIPE and the resulting precipitate was filtered off, washed with DIPE, and dried, yielding 2.5 g (3%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α,α-dimethylbenzeneacetonitrile (interm. 7).

e) A solution of intermediate (7) (0.107 mol) and *N*,*N*-bis(1-methylethyl)ethanamine (0.315 mol) in pyridine (500 ml) was stirred and heated to 80°C. H_2S was allowed to bubble through this solution for 24 hours at 80°C. H_2S gas inlet was stopped and the reaction mixture was stirred over the weekend at RT. The solvent was evaporated. CH_2Cl_2/CH_3OH (500 ml; 9:1) was added, and this mixture was poured out into 2 N HCl (1000 ml) at 0°C. The mixture was stirred for 10 minutes. The precipitate was filtered off and dried, yielding 23.2 g (64%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4]-α,α-dimethylbenzeneethanethioamide (interm. 8).

Example A3

Reaction under N2 atmosphere. A solution of intermediate (8)(0.0125 mol) and



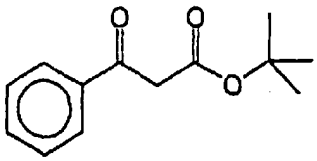
(0.0157 mol) in ethanol (60 ml) and DMF (30 ml; dried over molecular sieves) was stirred for 6.5 hours at 60 °C, then overnight at RT. The solvent was evaporated. The residue was taken up into water (100 ml) and this mixture was extracted with CH2Cl2 (100 ml). The separated organic layer was dried (MgSO4), filtered and the solvent evaporated, then co-evaporated with toluene. The residue (13 g) was purified by flash column chromatography over silica gel (eluent: CH2Cl2/CH3OH 100/0, then 99/1, ending with 98/2). The desired fractions were collected and the solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator. The residue (6.5 g) was crystallized from CH3CN. The precipitate was filtered off, washed with CH3CN and DIPE, then dried (vacuum, 50 °C), yielding 3.17 g (46.5 %) of ethyl-2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl]phenyl]-1-methylethyl]-4-phenyl-5-thiazoleacetate (intermediate 9) having a melting point of 148°C.

Example A4

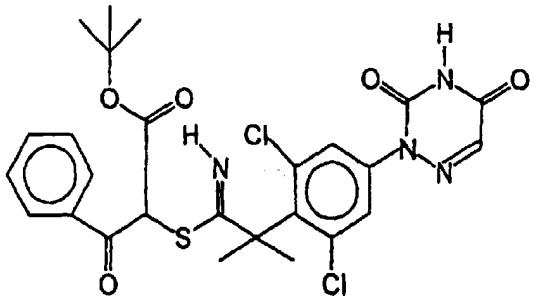
A mixture of intermediate (9) (0.00183 mol) and NaOH 1N (0.0055 mol) in CH_3OH (25 ml) and THF (25 ml) was stirred overnight at RT. The reaction mixture was acidified with 1N HCl (8 ml), and the product was taken up into EtOAc. The organic layer was washed with brine, dried, filtered and the solvent was evaporated. The residue was crystallized from CH_3CN. The precipitate was filtered off, washed with DIPE, and dried, yielding 0.8 g (79%) of 2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazoleacetic acid (intermediate (10)).

Example A5

First a solution of bromine (0.02 mol) in CH2Cl2 (20 ml) was added dropwise at 10°C under N2 flow to a mixture of a compound of formula



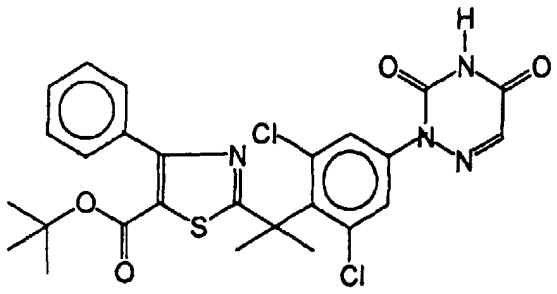
(0.0227 mol) in CH2Cl2 (50ml). The mixture was stirred at 10°C for 1 hour. H2O and solid K2CO3 were added. The organic layer was separated, dried (MgSO4), filtered and the solvent was evaporated. The reaction was carried out 4 times, using the same quantities and combining the residues yielding 14 g (51%) of 1,1-dimethylethyl α-bromo-β-oxo-benzenepropanoate. A mixture of intermediate (8) (0.0119 mol), 1,1-dimethylethyl α-bromo-β-oxo-benzenepropanoate (0.0137 mol) and K_2CO_3 (0.0357 mol) in CH_3CN (55ml) was stirred at room temperature for 3.5 hours. Ice and EtOAc were added. The mixture was acidified with HCl 3N. The organic layer was separated, dried (MgSO4), filtered and the solvent was evaporated. The product was used without further purification. Yielding: 8g of intermediate 11 having the formula



Example A6

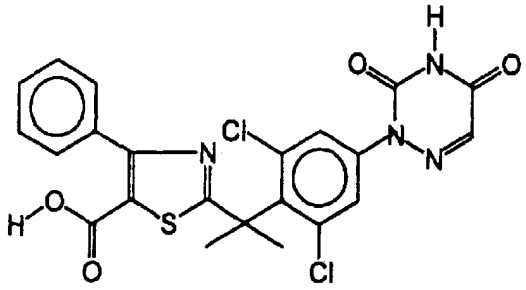
Intermediate (11) (0.0119 mol) and tert.-butanol (24g) were stirred and refluxed for 2 hours. The mixture was brought to room temperature. The solvent was evaporated. The residue was taken up in CH2Cl2. The organic solution was washed with H2O, dried (MgSO4), filtered and the solvent was evaporated. The residue (7.8g) was purified by column chromatography over silica gel (eluent: CH2Cl2/CH3OH 99/1; 15-40 µm). Two fractions were collected and their solvents were evaporated. Yielding: 2.66g (fraction 1) and 0.7g fraction 2 (50%). Fraction 2 was purified by column chromatography over C 18 (eluent: CH3OH/NH4OAc 0.5% 80/20; column: HYPERSIL C 18 3 µm). The pure fractions were collected and the solvent was

evaporated. Yielding: 0.45g of intermediate 12 having a melting point of 130°C and represented by the formula



Example A7

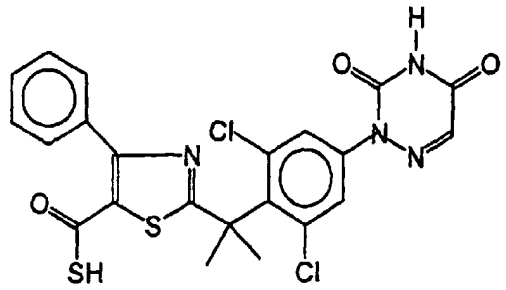
Intermediate 12 (0.00465 mol) was added portionwise at 0°C-10°C to trifluoroacetic acid (35ml). The mixture was stirred at room temperature for 3 hours and poured out into H2O. The precipitate was filtered off, washed with H2O and taken up in CH2Cl2. The organic layer was separated, dried (MgSO4), filtered and the solvent was evaporated. The residue (2.4g) was purified by column chromatography over silica gel (eluent: CH2Cl2/CH3OH/NH4OH 97/3/0.2; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH3CN. The precipitate was filtered off and dried. Yielding: 1.16g of intermediate 13 having a melting point of 232°C and represented by the formula



Example A8

1,1'-carbonylbis-1H-imidazole (0.0159 mol) was added portionwise at RT under N2 flow to a solution of intermediate (13) (0.00795 mol) in DMF (60 ml). The mixture was stirred at RT overnight. H2S was bubbled through the mixture for 1 hour. The mixture was stirred at RT for 1 hour, poured out into a sarurated NaCl solution and

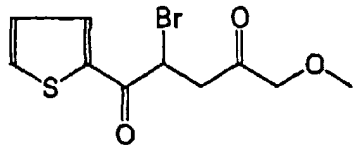
extracted twice with CH2Cl2. The combined organic layer was dried (MgSO4), filtered and the solvent was evaporated. The product, interm.14 represented by the formula



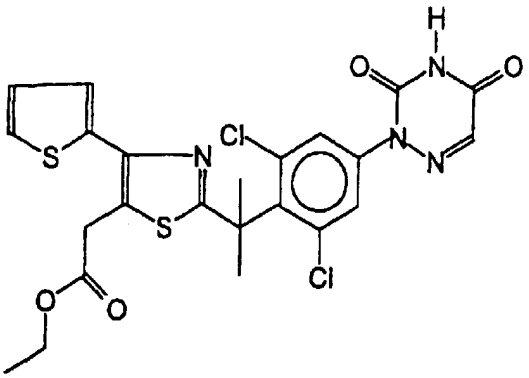
was used without further purification.

Example A9

A mixture of intermediate (8) (0.0158 mol) and

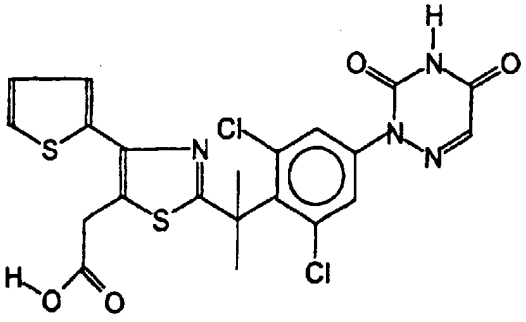


(0.0237 mol) in ethanol (60ml) and DMF (40ml) was stirred at 60°C for 4 hours. The solvent was evaporated. EtOAc was added. The organic solution was washed 3 times with H2O, dried (MgSO4), filtered and the solvent was evaporated. The residue (11.2g) was purified by column chromatography over silica gel (eluent: CH2Cl2/CH3OH 98/2; 15-40 μm). The desired fractions were collected and the solvent was evaporated. Yielding: 4.2g (47%). Part of this fraction (1.5g) was crystallized from petroleum ether and DIPE. The precipitate was filtered off and dried. Yielding: 1.15g of intermediate 15 having a melting point of 126°C and represented by the formula



Example A10

A mixture of intermediate (15) (0.0045 mol) and NaOH (0.0135 mol) in methanol (30ml) and THF (30ml) was stirred at room temperature for 12 hours, poured out on ice, acidified with HCl and extracted with EtOAc. The organic layer was separated, dried (MgSO4), filtered and the solvent was evaporated. The residue (2.2g) was purified by column chromatography over silica gel (eluent: CH2Cl2/CH3OH/NH4OH 95/5/0.1; 15-40 µm). The pure fractions were collected and the solvent was evaporated. Yielding: 1.5g (64%). Part of this fraction (1g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.5g of intermediate 16 having a melting point of 192°C and represented by the formula



Example A11

a) $NaOCH_3$ 30% (0.592 mol) was added to a solution of hydroxylamine hydrochloride (0.1085 mol) in CH_3OH (200 ml), stirred at RT. The mixture was stirred for 10 minutes. Intermediate (3) (0.0542 mol) was added portionwise and the resulting reaction mixture was stirred and refluxed overnight. The solvent was evaporated. The residue was partitioned between CH_2Cl_2 and water. The organic layer was separated,

dried, filtered and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed with DIPE, and dried, yielding 3.7 g of (26%) 4-amino-2,6-dichloro-N'-hydroxy-α,α-dimethylbenzeneethanimidamide (interm. 17).

b) A solution of intermediate (17) (0.0323 mol) and *N,N*-bis(methylethyl)ethanamine (0.0339 mol) in CH_2Cl_2 (190 ml) was stirred at 15°C. A solution of 2-methylbenzoyl chloride (0.0323 mol) in CH_2Cl_2 (10 ml) was added dropwise and the resulting reaction mixture was stirred for one hour. Water was added. The organic layer was separated, dried, filtered and the solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding 13.0 g of [1-amino-2-(4-amino-2,6-dichlorophenyl)-2-methylpropylidenyl]amino 2-methylbenzoate (interm. 18).

c) A solution of intermediate (18) (0.0323 mol) and *p*-toluenesulfonic acid (0.0323 mol) in DMSO (100 ml) was stirred for 30 minutes at 150°C. The reaction mixture was cooled. Water was added and this mixture was extracted with toluene. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by short column chromatography over silica gel (eluent: CH_2Cl_2). The desired fractions were collected and the solvent was evaporated. The concentrate was co-evaporated with EtOAc, yielding 11.7 g of 3,5-dichloro-4-[1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]benzenamine (interm. 19).

d) A solution of intermediate (19) (0.0302 mol) and HCl conc. (0.0906 mol) in acetic acid (100 ml) was stirred at 0°C. A solution of $NaNO_2$ (0.032 mol) in water (10 ml) was added dropwise at 0°C. The reaction mixture was stirred for 1 hour at 0°C. A powdered mixture of sodium acetate (0.0906 mol) and diethyl(1,3-dioxo-1,3-propanediyl)biscarbamate (0.0332 mol) was added portionwise. The mixture was allowed to warm to RT and stirred for 1 hour. Water was added and this mixture was extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated, yielding diethyl *N,N'*-[2-[[3,5-dichloro-4-[1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]hydrazono]-1,3-dioxo-1,3-propanediyl]-dicarbamate (interm. 20).

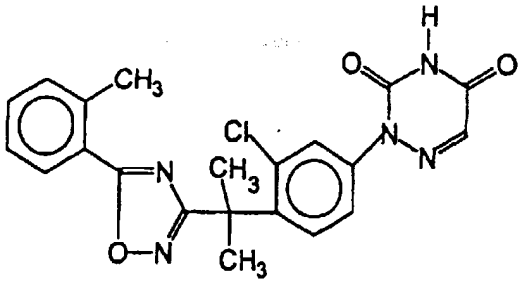
e) A solution of intermediate (20) (0.0302 mol) and sodium acetate (0.0302 mol) in acetic acid (200 ml) was stirred and refluxed for 3 hours. The reaction mixture was poured out into water and this mixture was extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding ethyl [[2-[3,5-dichloro-4-[1-[5-(2-methyl-

phenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-6-yl]carbonyl]carbamate (interm. 21).

f) A mixture of intermediate (21) (0.0302 mol) in HCl 36% (10 ml) and acetic acid (200 ml) was stirred and refluxed overnight. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated, yielding 16.3 g of 2-[3,5-dichloro-4-[1-[5-[2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 22).

Example A12

A mixture of intermediate (22) (0.0133 mol) in mercaptoacetic acid (7ml) was stirred at 175°C for 2 hours. The mixture was cooled, poured out into ice water, basified with K_2CO_3 and extracted with EtOAc. The organic layer was separated, washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1). The pure fractions were collected and the solvent was evaporated, yielding 2.2g (36%) of intermediate 23 represented by the formula

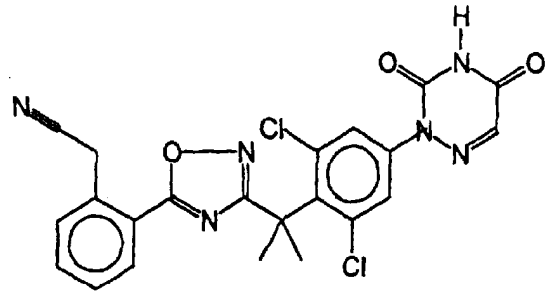


Example A13

A mixture of intermediate (23) (0.0011 mol), 1-bromo-2,5-pyrrolinedione (0.0011 mol) and dibenzoyl peroxide (catalytic quantity) in CCl_4 (30 ml) was stirred and refluxed for 3 hours. The mixture was allowed to cool to RT. The mixture was filtered over dicalite and the filtrate contained 2-[4-[1-[5-[2-(bromomethyl)phenyl]-1,2,4-oxadiazol-3-yl]-1-methylethyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (intermediate 24).

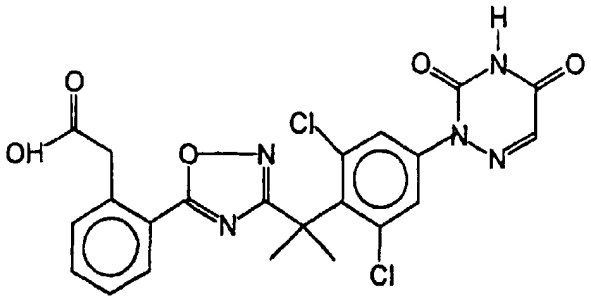
Example A14

A solution of intermediate (24) (0.017 mol) and KCN (0.034 mol) in ethanol (100 ml) and H2O (30 ml) was stirred for 8 hours at 60°C. The solvent was evaporated under reduced pressure. The residue was taken up into CH2Cl2, then washed with water, dried (MgSO4), filtered and the solvent was evaporated. Yield: 8.2 g of interm.25 represented by the formula



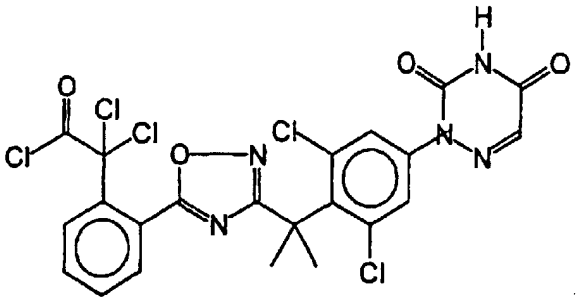
Example A15

A solution of intermediate (25) (0.017 mol) in HOAc (50 ml), H_2SO_4 (50 ml) and H_2O (50 ml) was stirred and refluxed for 2 hours. The reaction mixture was poured out into ice-water and the resulting precipitate was filtered off, washed, then dissolved in CH2Cl2. The organic solution was dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH2Cl2/CH3OH 95/5). The desired fractions were collected and the solvent was evaporated. The residue was purified by HPLC over RP BDS Hyperprep C18 (100 Å =, 8 µm; gradient elution with (0.5% NH4OAc in water/CH3CN 90/10)/CH3OH/CH3CN). The pure fractions were collected and the solvent was evaporated. The residue was stirred in hexane, filtered off and dried (vacuum, 60 °C). Yield: 0.084 g of intermediate 26 represented by the formula



Example A16

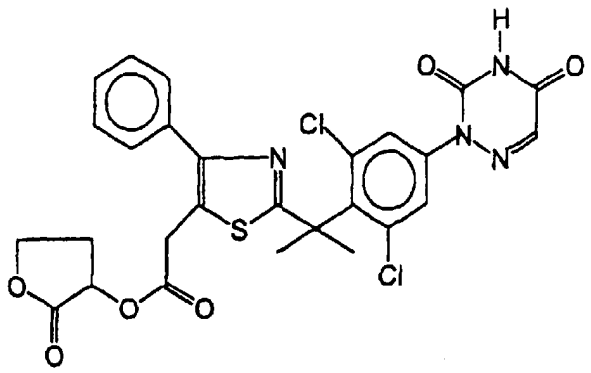
A solution of intermediate (26) (0.0014 mol) in SOCl2 (15 ml) was stirred and refluxed for 1 hour. SOCl2 was evaporated under reduced pressure. Toluene was added and azeotroped on the rotary evaporator, yielding 100% of intermediate 27 represented by the formula



B. Preparation of the final compounds

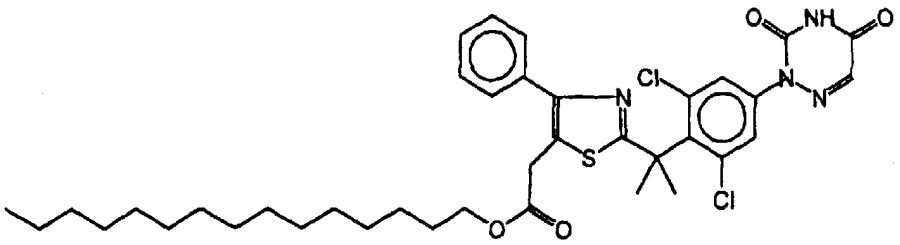
Example B1

A mixture of 3-bromodihydro-2(3H)-furanone (0.0081 mol) in DMF (16ml) was added dropwise at room temperature to a mixture of intermediate (10)(0.00773 mol) and $NaHCO_3$ (0.0081 mol) in DMF (30ml). The mixture was stirred at 70°C for 5 hours and brought to room temperature. H2O and a saturated NaCl solution were added. The mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO4), filtered and the solvent was evaporated. The residue (5g) was purified by column chromatography over silica gel (eluent: CH2Cl2/CH3OH 98/2; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue was taken up in DIPE. The precipitate was filtered off and dried. Yielding: 1.24g compound 1 having a melting point of 72°C and represented by the formula



Example B2

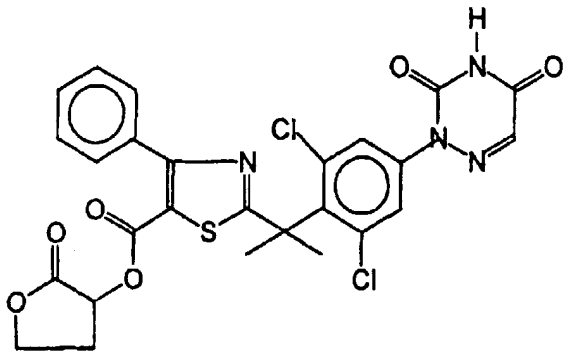
A solution of 1-bromopentadecane (0.0051 mol) in DMF (18ml) was added dropwise at room temperature to a mixture of intermediate (10) (0.00483 mol) and $NaHCO_3$ (0.0051 mol) in DMF (10ml). The mixture was stirred at 70°C for 5 hours and at 45°C overnight, then brought to room temperature. H2O and NaCl was added. The mixture was extracted with EtOAc. The organic layer was separated, washed with a saturated NaCl solution, dried (MgSO4), filtered and the solvent was evaporated. The residue (3.8g) was purified by column chromatography over silica gel (eluent: CH2Cl2/CH3OH 98/2; 15-40 µm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.49g compound 2 having a melting point of 80°C and represented by the formula



Example B3

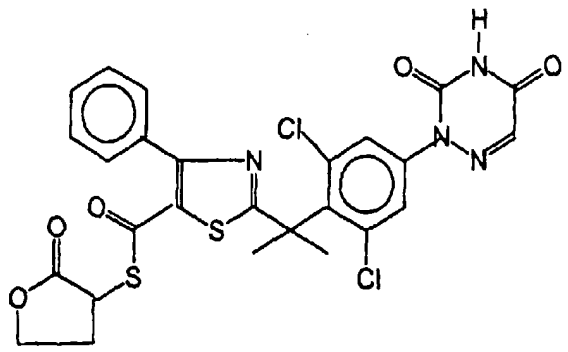
A solution of 3-bromodihydro-2(3H)-furanone (0.0073 mol) in DMF (12ml) was added dropwise at RT to a mixture of intermediate (13) (0.00695 mol) and $NaHCO_3$ (0.0073 mol) in DMF (22ml). The mixture was stirred at 70°C for 2.5 hours, brought to RT and poured out into H2O. The precipitate was filtered off and taken up in CH2Cl2. The organic layer was separated, washed with H2O, dried (MgSO4), filtered and the solvent was evaporated. The residue (5.4g) was purified by column chromatography over silica

gel (eluent: CH2Cl2/CH3OH 98/2; 15-40 µm). The desired fractions were collected and the solvent was evaporated. The residue was crystallized from CH3CN, diethyl ether and DIPE. The precipitate was filtered off and dried. Yielding: 1.3g. This fraction was recrystallized from CH3CN, 2-propanone and diethyl ether. The precipitate was filtered off and dried. Yielding: 0.89g compound 3 having a melting point of 208°C and represented by the formula



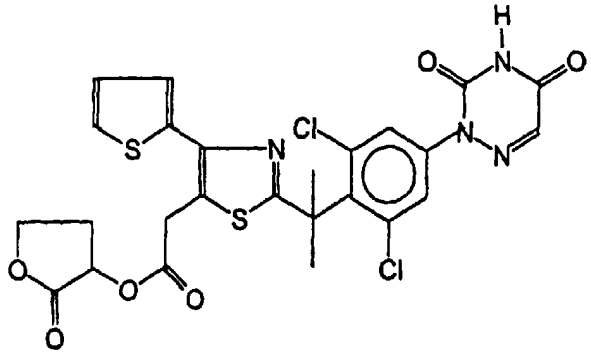
Example B4

$NaHCO_3$ (0.00835 mol) was added dropwise at 5°C under N2 flow to a mixture of intermediate (14) (0.00795 mol) in DMF (22ml). Then a solution of 3-bromodihydro-2(3H)-furanone (0.00835 mol) in DMF (12ml) was added dropwise. The mixture was brought to RT and stirred at RT for 30 min and then poured out into H2O and a saturated NaCl solution. A small amount of HCl 3N was added. The precipitate was filtered off and taken up in CH2Cl2. The organic layer was separated, dried (MgSO4), filtered and the solvent was evaporated. The residue (5.1g) was purified by column chromatography over silica gel (eluent: CH2Cl2/CH3OH 98.5/1.5; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH3CN, diethyl ether and DIPE. The precipitate was filtered off and dried. The residue was recrystallized from CH3CN, diethyl ether and DIPE. The precipitate was filtered off and dried. Yielding: 0.85g compound 4 having a melting point of 212°C and represented by the formula



Example B5

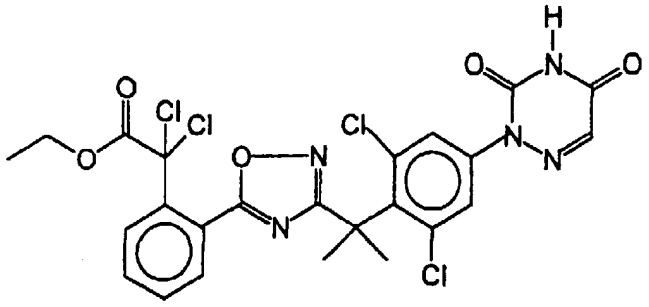
A mixture of 3-bromodihydro-2(3H)-furanone (0.00172 mol) in DMF (5ml) was added dropwise at RT to a mixture of intermediate (16) (0.00172 mol) and $NaHCO_3$ (0.00172 mol) in DMF (5ml). The mixture was stirred at 70°C for 5 hours, poured out into H2O and a saturated NaCl solution and extracted with EtOAc. The organic layer was separated, washed several times with H2O, dried (MgSO4), filtered and the solvent was evaporated. The residue (1.2g) was purified by column chromatography over silica gel (eluent: CH2Cl2/CH3OH 98/2; 15-40 µm). The desired fractions were collected and the solvent was evaporated. The residue was purified again by column chromatography over silica gel (eluent: CH2Cl2/2-propanol 97/3; 15-40 µm). The desired fractions were collected and the solvent was evaporated. Yielding: 0.13g compound 5 having a melting point of 110°C and represented y the formula



Example B6

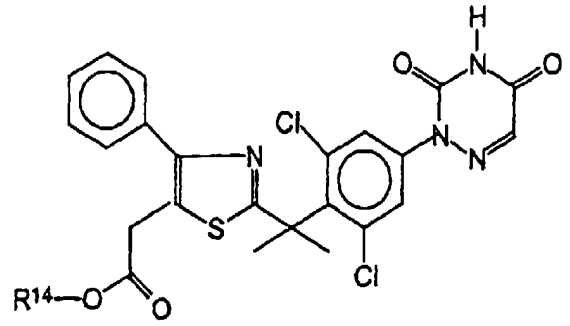
A solution of intermediate (27) (0.001 mol) in ethanol (15 ml) and dichloromethane (15 ml) was stirred and refluxed for one hour. The solvent was evaporated under reduced pressure. The residue was dissolved in CH2Cl2, washed with water, dried (MgSO4),

filtered and the solvent was evaporated. The residue was purified by HPLC over Hyperprep C18 (eluent: ((0.5% NH4OAc in H2O)/CH3CN 90/10)/CH3CN (0 min) 80/20, (44 min) 20/80, (57-61 min) 0/100) . The desired fractions were collected and the solvent was evaporated. The residue was stirred in hexane, filtered off, washed and dried (vacuum, 60 °C). Yield: 0.059 g compound 6 having a melting point of 157°C and represented by the formula



Example B7

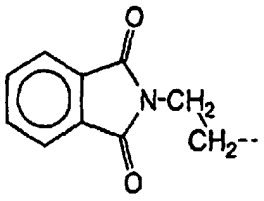
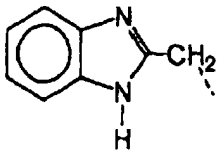
A mixture of intermediate (10) (0.00387 mol) and 1,1'-carbonylbis-1H-imidazole (0.0058 mol) in dichloromethane (40ml) was stirred at RT for 90 minutes, then cyclohexylmethanol (0.0058 mol) was added. The mixture was stirred at RT overnight, diluted with CH2Cl2 and washed twice with an aqueous solution of NaCl. The organic layer was separated, dried (MgSO4), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH2Cl2/EtOAc 50/50). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from EtOAc. The precipitate was filtered off, washed with DIPE and dried at 50°C overnight. Yielding: 1.43g compound 7 with a melting point of 180°C and represented by the formula

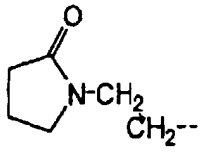
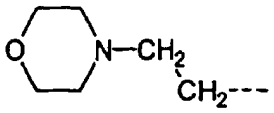


IA

wherein R^{14} is cyclohexylmethyl.

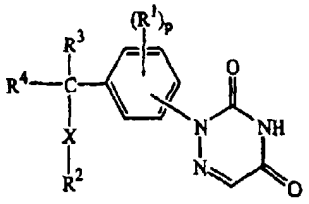
The following table 1 lists compounds of formula (IA) which were prepared according to the same procedure.

COMPOUND NO.	R^{14}	MELTING POINT (°C)
8		
9	Isopentyl	148
10	2-phenyl-ethyl	130
11	3-phenyl-n-propyl	114
12	2-(N,N'-diisopropylamino)-ethyl	136
13	2-cyano-ethyl	179
14		
15	3-cyclohexyl-n-propyl	130

16	4-phenyl-n-butyl	128
17	Cyclopropylmethyl	
18	3-cyclopropyl-n-propyl	
19		
20		

Claims

1. A compound having the formula



(I)

a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

p represents an integer being 0, 1, 2, 3 or 4;

X represents O, S, NR^5 or a direct bond or-X-R^2 taken together may represent cyano;

Y represents O, S, NR^5, or $S(O)_2$;

each R^1 independently represents C(=0)·Z-R^{14}, C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or C_{1-4}alkyl substituted with C(=0)-Z·R^{14}, Het^3, R^6 or NR^7R^8;

R^2 represents Het^1, C_{3-7}cycloalkyl optionally substituted with C(=0)-Z-R^{14}, C_{1-6}alkyl or C_{1-6}alkyl substituted with one or two substituents selected from C(=0)·Z-R^{14}, hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxy optionally substituted with C(=0)-Z-R^{14}, C_{1-6}alkylsulfonyloxy, C_{3-7}cycloalkyl optionally substituted with C(=0)-Z-R^{14}, aryl, aryloxy, arylthio, Het^1, Het^1oxy and Het^1thio; and if X is O, S or NR^5, then R^2 may also represent aminothiocarbonyl, C_{1-4}alkylcarbonyl optionally substituted with C(=0)-Z-R^{14}, C_{1-4}alkylthiocarbonyl optionally substituted with C(=0)-Z-R^{14}, arylcarbonyl, arylthiocarbonyl, Het^1carbonyl or Het^1thiocarbonyl;

R^3 represents hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl;

R^4 represents hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl; or

R^3 and R^4 taken together form a C_{2-6}alkanediyl;

R^5 represents hydrogen or C_{1-4}alkyl;

each R^6 independently represents C_{1-6}alkylsulfonyl, aminosulfonyl, mono- or di(C_{1-4}alkyl)-aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC_{1-6}alkylsulfonyl, C_{1-6}alkylsulfinyl, phenylC_{1-4}alkylsulfonyl, piperazinylsulfonyl, aminopiperidinyl-sulfonyl, piperidinylaminosulfonyl, *N*-C_{1-4}alkyl-*N*-piperidinylaminosulfonyl or mono-or di(C_{1-4}alkyl)aminoC_{1-4}alkylsulfonyl;

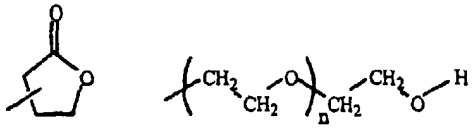
each R^7 and each R^8 are independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, arylcarbonyl, Het^3carbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-Z-R^{14}, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, Het^3, Het^4 and R^6;

R^9 and R^{10} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, Het^3carbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-Z-R^{14}, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, Het^3, Het^4 and R^6;

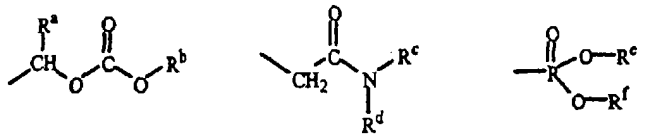
each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4}alkyloxy optionally substituted with C(=O)-Z-R^{14}, formyl, trihaloC_{1-4}alkylsulfonyloxy, R^6, NR^7R^8, C(=O)$NR^{15}R^{16}$, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, aryl, aryloxy, arylcarbonyl, C_{3-7}cycloalkyl optionally substituted with C(=O)-Z-R^{14}, C_{3-7}cycloalkyloxy optionally substituted with C(=O)-Z-R^{14}, phthalimide-2-yl, Het^3 and C(=O)Het^3;

R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-Z-R^{14}, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14} and R^6;

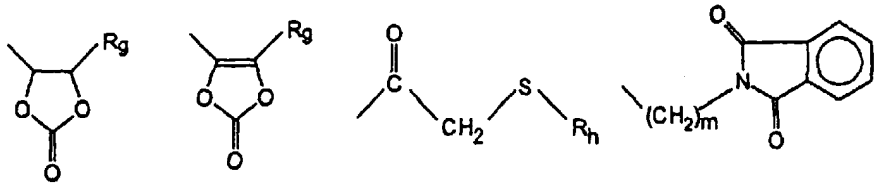
each R^{14} independently represents C_{1-4} alkyl substituted with one or more substituents selected from phenyl, di- C_{1-4}alkylamino, cyano, Het^1 and C_{3-7} cycloalkyl, hydrogen, C_{1-20}acyl (having a straight or branched, saturated or unsaturated hydrocarbon chain having 1 to 20 carbon atoms), C_{1-20}alkyl, C_{3-7}cycloalkyl, polyhaloC_{1-20}alkyl or a radical of formula



(a) (b)



(c) (d) (e)



(h) (i) (j) (k)

wherein n is 0 to 5 and m is 1 to 4;

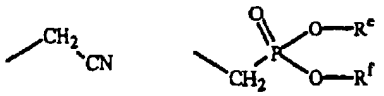
R^a, R^b, R^c, R^d, R^e and R^f are each independently hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl; or

R^e and R^f taken together may form $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-CH_2-$;

R_g and R_h are each independently C_{1-4} alkyl;

each Z independently represents O, S, NH, $-CH_2-O-$ or $-CH_2-S-$ whereby $-CH_2-$ is attached to the carbonyl group;

$-Z-R^{14}$ taken together form a radical of formula



(f) (g)

R^{15} and R^{16} are each independently selected from dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, $-C(=O)-Z-R^{14}$, arylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, pyridinylC_{1-4}alkyl, Het^3, Het^4 or R^6;

aminocarbonylmethylene or mono-or di(C_{1-4}alkyl)aminocarbonylmethylene;

aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, cyano, halo, hydroxy, C_{1-4}alkyl, C_{3-7}cyclo-

alkyl, C_{1-4}alkyloxy, formyl, polyhaloC_{1-4}alkyl, NR^9R^{10}, $C(=O)NR^9R^{10}$, $C(=O)$-Z-R^{14}, R^6, -O-R^6, phenyl, Het^3, $C(=O)Het^3$ and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C_{1-4}alkyloxy, $C(=O)$-Z-R^{14}, -Y-C_{1-4}alkanediyl-$C(=O)$-Z-R^{14}, Het^3 or NR^9R^{10};

Het^1 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]-thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from Het^2 and R^{11};

Het^2 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^4, R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from Het^4 and R11;

Het^3 represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4}alkyl,

C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, piperidinyl, $NR^{12}R^{13}$, C(=O)-Z-R^{14}, R^6 and C_{1-4}alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4}alkyloxy, phenyl, C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, R^6 and $NR^{12}R^{13}$;

Het^4 represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl

provided however that

- R^2 is other than C_{1-6} alkyloxycarbonylC_{1-6}alkyl, aminocarbonyl; and
- R^7, R^8, R^9 and R^{10} are other than aminocarbonyl, C_{1-4}alkylcarbonyloxy- C_{1-4}alkylcarbonyl, hydroxy C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl C(=O)-O-R^{14}, C_{1-4}alkanediylC(=O)-O-R^{14} and –Y-C_{1-4}alkanediylC(=O)-O-R^{14}; and
- R^{12} and R^{13} are other than C_{1-4}alkylcarbonyloxy-C_{1-4}alkylcarbonyl, hydroxy C_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonylcabonyl; and
- R^{11} is other than C(=O)-O-R^{14}, Y-C_{1-4}alkanediyl – C(=O)-OR^{14}, $C(=O)NH_2$, $C(=O)NHC_{1-4}$alkyl or $C(=O)NHC_{3-7}$cycloalkyl; and
- R^{14} is other than hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, aminocarbonylmethylene, mono- or di (C_{1-4}alkyl) aminocarbonylmethylene in the event Z is 0; and
- R^{15} and R^{16} are other than aminocarbonyl, C_{1-4}alkylcarbonyloxy-C_{1-4}alkylcarbonyl, hydroxy C_{1-4}alkylcarbonyl or C_{1-4}alkyloxycarbonylcarbonyl; and
- Aryl is other than phenyl substituted with C(=O)-O-R^{14} $C(=O)NH_2$, $C(=O)NHC_{1-4}$alkyl, $C(=O)NHC_{3-7}$cycloalkyl and/or with C_{1-4}alkyl substituted with C(=O)-O-R^{14} or Y-C_{1-4}alkanediyl – C(=O)-O-R^{14}; and
- Het^3 is other than a monocyclic heterocycle substituted with C(=O)-O-R^{14} and/or with C_{1-4}alkyl substituted with C(=O)-O-R^{14} and/or Y-C_{1-4}alkanediyl – (=O)-O-R^{14}; and
- The said compound of formula (I) contains at least one – C(=O)-Z-R^{14} moiety.

2. A compound as claimed in claim 1 wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R^2, R^3 and R^4 substituents.

3. A compound as claimed in claims 1 or 2 wherein R^2 is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, wherein said monocyclic

heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with Het^2 or R^{11}.

4. A compound as claimed in any one of claims 1 to 3 wherein R^3 and R^4 are both methyl and -X-R^2 is Het^1.

5. A compound as claimed in any one of claims 1 to 4 wherein p is 1 or 2 and each R^1 is chloro.

6. A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5.

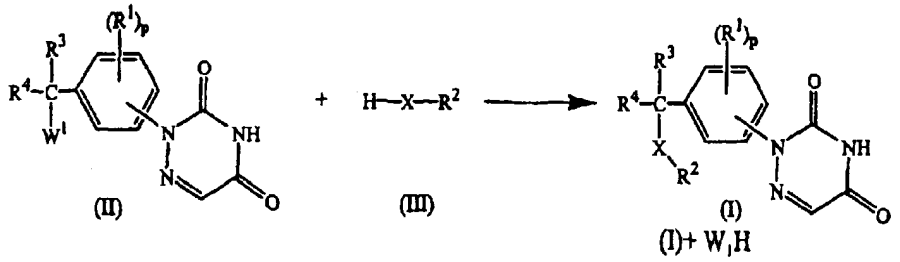
7. A process for preparing a composition as claimed in claim 6, , wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined in any one of claims 1 to 5.

8. A compound as claimed in any one of claims 1 to 5 for use as a medicine.

9. Use of a compound as claimed in any one of claims 1 to 5 in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases.

10. A process for preparing a compound as claimed in claim 1, characterized by,

a) reacting an intermediate of formula (II) wherein W^1 is a suitable leaving group with an appropriate reagent of formula (III) optionally in a reaction-inert solvent and optionally in the presence of a base at a temperature ranging between - 70°C and reflux temperature;

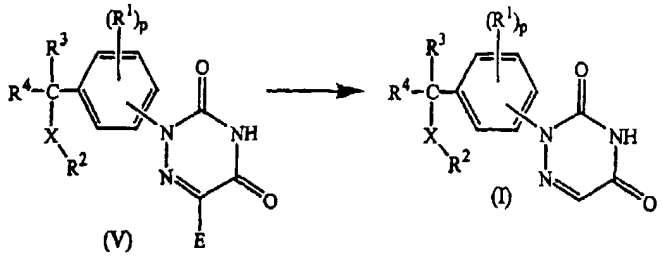


(II) (III) (I)

(I)+ W,H

wherein R^1 R^2, R^3, R^4, p and X are as defined in claim 1 or;

b) eliminating the group E of a triazinedione of formula (V)



(V) (I)

wherein E is an appropriate electron attracting group and R^1, R^2, R^4, X and p are as defined in claim 1;

and, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and also, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

11. A process of marking a receptor comprising the steps of

a) radiolabelling a compound as defined in claim 1;

b) administering said radiolabelled compound to biological material,

c) detecting the emissions from the radiolabelled compound.

12. A process of imaging an organ, characterized by, administering a sufficient amount of a radiolabelled compound of formula (I) in an appropriate composition, and detecting the emissions from the radioactive compound.

==== BIBLIOGRAPHIC DATA OF APPLICATION: 99870170.0 (= EP application)

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Title: Non steroidal IL-5 inhibitors, processes for their preparation and pharmaceutical compositions comprising them(11.11.11)

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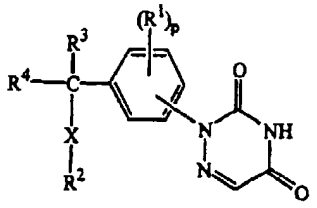
ABSTRACT

NON-STEROIDAL IL-5 INHIBITORS, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

The present invention is concerned with the compounds of formula



(I)

the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein p is 0 to 4; X is O, S, NR^5 or a direct bond; Y is O, S, NR^5 or $S(O)_2$; R^1 independently is C (=O)-Z-R^{14} ,C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, NR^7R^8 or substituted C_{1-4}alkyl; R^2 is Het^1, C_{3-7}cycloalkyl or optionally substituted C_{1-6}alkyl and if X is O, S or NR^5, then R^2 may also represent C(=O)-Z-R^{14}, aminothiocarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkylthiocarbonyl, arylcarbonyl, arylthiocarbonyl, Het^1carbonyl or Het^1thiocarbonyl; R^3 and R^4 independently are hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl or R^3 and R^4 together form a C_{2-6}alkanediyl; R^5 is hydrogen or C_{1-4}alkyl; R^7 and R^8 are independently hydrogen, optionally substituted C_{1-4}alkyl, aryl, a carbonyl containing moiety, C_{3-7}cycloalkyl, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14} or Het^3; R^{14} is hydrogen, C_{1-20}alkyl, C_{3-7}cycloalkyl, C_{1-20} acyl or another radical; Z is O, S, NH, -CH_2O- or -CH_2S- whereby -CH_2- is attached to the carbonyl group; aryl is optionally substituted phenyl; Het^1, Het^2, Het^3 and Het^4 are optionally substituted heterocycles, provided that the said compounds contain at least one -C(=O)-Z-R_{14} moiety; to processes for their preparation and pharmaceutical compositions comprising them. It further relates to their use as a medicine.